```
FILE 'HOME' ENTERED AT 08:03:00 ON 15 APR 2010

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY     SESSION
FULL ESTIMATED COST                                    0.22        0.22

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
      AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
      CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
      DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 08:03:18 ON 15 APR 2010

63 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s retin? (s) (pml/rar or pml-rar)
         12*  FILE ADISCTI
          2*  FILE ADISINSIGHT
          1*  FILE ADISNEWS
          7*  FILE AGRICOLA
          1*  FILE ANABSTR
          0*  FILE ANTE
          0*  FILE AQUALINE
          0*  FILE AQUASCI
         32*  FILE BIOENG
        233*  FILE BIOSIS
          7*  FILE BIOTECHABS
          7*  FILE BIOTECHDS
        289*  FILE BIOTECHNO
          6*  FILE CABA
        430*  FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
          8*  FILE CONFSCI
          0*  FILE CROPB
          0*  FILE CROPU
          0*  FILE DDFB
<------User Break------>

=> s retin? (s) (pml/rar or pml-rar#)
         14*  FILE ADISCTI
          2*  FILE ADISINSIGHT
          2*  FILE ADISNEWS
          7*  FILE AGRICOLA
          1*  FILE ANABSTR
          0*  FILE ANTE
          0*  FILE AQUALINE
          0*  FILE AQUASCI
         47*  FILE BIOENG
        280*  FILE BIOSIS
         12*  FILE BIOTECHABS
         12*  FILE BIOTECHDS
        327*  FILE BIOTECHNO
          6*  FILE CABA
        473*  FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
          8*  FILE CONFSCI
```

```
          0*  FILE CROPB
          0*  FILE CROPU
          0*  FILE DDFB
         60*  FILE DDFU
         53*  FILE DGENE
         17*  FILE DISSABS
          0*  FILE DRUGB
          0*  FILE DRUGMONOG2
         90*  FILE DRUGU
          5*  FILE EMBAL
        305*  FILE EMBASE
        397*  FILE ESBIOBASE
          0*  FILE FOMAD
          0*  FILE FROSTI
          0*  FILE FSTA
          3*  FILE GENBANK
  34 FILES SEARCHED...
          0*  FILE HEALSAFE
         10*  FILE IFIPAT
          0*  FILE IMSDRUGNEWS
          4*  FILE IMSPRODUCT
          1*  FILE IMSRESEARCH
          0*  FILE KOSMET
        204*  FILE LIFESCI
        162*  FILE MEDLINE
          1*  FILE NTIS
          0*  FILE OCEAN
        284*  FILE PASCAL
          0*  FILE PCTGEN
         13*  FILE PROMT
          0*  FILE PROUSDDR
          0*  FILE PS
          0*  FILE RDISCLOSURE
        276*  FILE SCISEARCH
          0*  FILE SYNTHLINE
        241*  FILE TOXCENTER
          0*  FILE USGENE
        194*  FILE USPATFULL
          0*  FILE USPATOLD
         36*  FILE USPAT2
          0*  FILE VETB
          0*  FILE VETU
          0*  FILE WATER
          6*  FILE WPIDS
          0*  FILE WPIFV
  62 FILES SEARCHED...
          6*  FILE WPINDEX

  35 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L1   QUE RETIN? (S) (PML/RAR OR PML-RAR#)

=> s L1 (s) degrad?

          0*  FILE ADISCTI
          1*  FILE ADISINSIGHT
          0*  FILE ADISNEWS
          2*  FILE AGRICOLA
          0*  FILE ANABSTR
          0*  FILE ANTE
          0*  FILE AQUALINE
```

```
         0*  FILE AQUASCI
         7*  FILE BIOENG
        18*  FILE BIOSIS
         1*  FILE BIOTECHABS
         1*  FILE BIOTECHDS
        30*  FILE BIOTECHNO
         1*  FILE CABA
        31*  FILE CAPLUS
         0*  FILE CEABA-VTB
         0*  FILE CIN
         1*  FILE CONFSCI
         0*  FILE CROPB
         0*  FILE CROPU
         0*  FILE DDFB
         8*  FILE DDFU
         0*  FILE DGENE
 23 FILES SEARCHED...
         0*  FILE DISSABS
         0*  FILE DRUGB
         0*  FILE DRUGMONOG2
        15*  FILE DRUGU
         0*  FILE EMBAL
        30*  FILE EMBASE
        58*  FILE ESBIOBASE
         0*  FILE FOMAD
         0*  FILE FROSTI
         0*  FILE FSTA
         0*  FILE GENBANK
         0*  FILE HEALSAFE
         0*  FILE IFIPAT
         0*  FILE IMSDRUGNEWS
         0*  FILE IMSPRODUCT
         0*  FILE IMSRESEARCH
         0*  FILE KOSMET
        22*  FILE LIFESCI
        10*  FILE MEDLINE
         0*  FILE NTIS
         0*  FILE OCEAN
        37*  FILE PASCAL
         0*  FILE PCTGEN
         2*  FILE PROMT
         0*  FILE PROUSDDR
         0*  FILE PS
         0*  FILE RDISCLOSURE
        27*  FILE SCISEARCH
         0*  FILE SYNTHLINE
        12*  FILE TOXCENTER
         0*  FILE USGENE
        44*  FILE USPATFULL
         0*  FILE USPATOLD
         9*  FILE USPAT2
         0*  FILE VETB
         0*  FILE VETU
         0*  FILE WATER
         1*  FILE WPIDS
         0*  FILE WPIFV
         1*  FILE WPINDEX

 24 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L2   QUE L1 (S) DEGRAD?
```

```
=> s L3 (s) (apl or (acute (2a) promylelocytic))
L3 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s L2 (s) (apl or (acute (2a) promylelocytic))
          0*  FILE ADISCTI
          1*  FILE ADISINSIGHT
          0*  FILE ADISNEWS
          2*  FILE AGRICOLA
          0*  FILE ANABSTR
          0*  FILE ANTE
          0*  FILE AQUALINE
          0*  FILE AQUASCI
          6*  FILE BIOENG
          6*  FILE BIOSIS
          0*  FILE BIOTECHABS
          0*  FILE BIOTECHDS
         26*  FILE BIOTECHNO
          1*  FILE CABA
          9*  FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
          0*  FILE CONFSCI
          0*  FILE CROPB
          0*  FILE CROPU
          0*  FILE DDFB
          4*  FILE DDFU
          0*  FILE DGENE
  23 FILES SEARCHED...
          0*  FILE DISSABS
          0*  FILE DRUGB
          0*  FILE DRUGMONOG2
          8*  FILE DRUGU
          0*  FILE EMBAL
         10*  FILE EMBASE
         44*  FILE ESBIOBASE
          0*  FILE FOMAD
          0*  FILE FROSTI
          0*  FILE FSTA
          0*  FILE GENBANK
          0*  FILE HEALSAFE
          0*  FILE IFIPAT
          0*  FILE IMSDRUGNEWS
          0*  FILE IMSPRODUCT
          0*  FILE IMSRESEARCH
          0*  FILE KOSMET
         18*  FILE LIFESCI
          4*  FILE MEDLINE
          0*  FILE NTIS
          0*  FILE OCEAN
         25*  FILE PASCAL
          0*  FILE PCTGEN
          1*  FILE PROMT
          0*  FILE PROUSDDR
          0*  FILE PS
          0*  FILE RDISCLOSURE
          8*  FILE SCISEARCH
          0*  FILE SYNTHLINE
          4*  FILE TOXCENTER
```

```
          0*  FILE USGENE
         42*  FILE USPATFULL
  55 FILES SEARCHED...
          0*  FILE USPATOLD
          9*  FILE USPAT2
          0*  FILE VETB
          0*  FILE VETU
          0*  FILE WATER
          1*  FILE WPIDS
          0*  FILE WPIFV
          1*  FILE WPINDEX

  21 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L3   QUE L2 (S) (APL OR (ACUTE (2A) PROMYLELOCYTIC))

=> s L3 (s) (cancer or neoplas## or tumor?)
          0*  FILE ADISCTI
          1*  FILE ADISINSIGHT
          0*  FILE ADISNEWS
          0*  FILE AGRICOLA
          0*  FILE ANABSTR
          0*  FILE ANTE
          0*  FILE AQUALINE
          0*  FILE AQUASCI
          4*  FILE BIOENG
          0*  FILE BIOSIS
          0*  FILE BIOTECHABS
          0*  FILE BIOTECHDS
          4*  FILE BIOTECHNO
          0*  FILE CABA
          0*  FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
          0*  FILE CONFSCI
          0*  FILE CROPB
          0*  FILE CROPU
          0*  FILE DDFB
  21 FILES SEARCHED...
          0*  FILE DDFU
          0*  FILE DGENE
  23 FILES SEARCHED...
          0*  FILE DISSABS
          0*  FILE DRUGB
          0*  FILE DRUGMONOG2
          1*  FILE DRUGU
          0*  FILE EMBAL
          0*  FILE EMBASE
         13*  FILE ESBIOBASE
          0*  FILE FOMAD
          0*  FILE FROSTI
          0*  FILE FSTA
          0*  FILE GENBANK
          0*  FILE HEALSAFE
          0*  FILE IFIPAT
          0*  FILE IMSDRUGNEWS
          0*  FILE IMSPRODUCT
          0*  FILE IMSRESEARCH
          0*  FILE KOSMET
          8*  FILE LIFESCI
  41 FILES SEARCHED...
```

```
          0*  FILE MEDLINE
          0*  FILE NTIS
          0*  FILE OCEAN
          5*  FILE PASCAL
          0*  FILE PCTGEN
          0*  FILE PROMT
          0*  FILE PROUSDDR
          0*  FILE PS
          0*  FILE RDISCLOSURE
          0*  FILE SCISEARCH
          0*  FILE SYNTHLINE
          0*  FILE TOXCENTER
          0*  FILE USGENE
  54 FILES SEARCHED...
         16*  FILE USPATFULL
          0*  FILE USPATOLD
          2*  FILE USPAT2
          0*  FILE VETB
          0*  FILE VETU
          0*  FILE WATER
          0*  FILE WPIDS
          0*  FILE WPIFV
          0*  FILE WPINDEX

    9 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L4   QUE L3 (S) (CANCER OR NEOPLAS## OR TUMOR?)

=> d rank

F1           16*  USPATFULL
F2           13*  ESBIOBASE
F3            8*  LIFESCI
F4            5*  PASCAL
F5            4*  BIOENG
F6            4*  BIOTECHNO
F7            2*  USPAT2
F8            1*  ADISINSIGHT
F9            1*  DRUGU


=> fil f2, f3, f5, f6
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     6.90       7.12

FILE 'ESBIOBASE' ENTERED AT 08:09:24 ON 15 APR 2010
COPYRIGHT (C) 2010 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'LIFESCI' ENTERED AT 08:09:24 ON 15 APR 2010
COPYRIGHT (C) 2010 Cambridge Scientific Abstracts (CSA)


FILE 'BIOENG' ENTERED AT 08:09:24 ON 15 APR 2010
COPYRIGHT (C) 2010 Cambridge Scientific Abstracts (CSA)

FILE 'BIOTECHNO' ENTERED AT 08:09:24 ON 15 APR 2010
COPYRIGHT (C) 2010 Elsevier Science B.V., Amsterdam. All rights reserved.

=> s L4
'RAR' IS NOT A VALID FIELD CODE
```

```
'RAR' IS NOT A VALID FIELD CODE
'RAR' IS NOT A VALID FIELD CODE
'RAR' IS NOT A VALID FIELD CODE
L5          29 L4

=> dup rem L5
PROCESSING COMPLETED FOR L5
L6           14 DUP REM L5 (15 DUPLICATES REMOVED)

=> s L6 and py,2004
L7            0 L6 AND PY,2004

=> s L6 and py<2004
L8            6 L6 AND PY<2004

=> d L8 ibib abs 1-8

L8     ANSWER 1 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on
       STN
ACCESSION NUMBER:         2001269487   ESBIOBASE <<LOGINID::20100415>>
TITLE:                    Pathways of retinoic acid- or arsenic trioxide-induced
                          PML/RARα catabolism, role of oncogene degradation
                          in disease remission
AUTHOR(S):                Zhu, J.; Lallemand-Breitenbach, V.; De The, H.
CORPORATE SOURCE:         Zhu, J.; Lallemand-Breitenbach, V.; De The, H.
                          (Laboratoire associe No. 11, Affilie a l'Universite de
                          Paris VII, Hopital St.Louis, 1, Av. C. Vellefaux, 75475
                          Paris Cedex 10 (FR))
SOURCE:                   Oncogene (29 Oct 2001) Volume 20, Number 49
                          REV. IIS. 6, pp. 7257-7265, 84 refs.
                          CODEN: ONCNES  ISSN: 0950-9232
                          DOI: 10.1038/sj.onc.1204852
COUNTRY OF PUBLICATION:   United Kingdom
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
SUMMARY LANGUAGE:         English
ENTRY DATE:               Entered STN: 1 Feb 2009
                          Last updated on STN: 1 Feb 2009
AN     2001269487   ESBIOBASE <<LOGINID::20100415>>
AB     Although there is evidence to suggest that PML/RAR
       α expression is not the sole genetic event required for the
       development of acute promyelocytic leukemia (APL), there is
       little doubt that the fusion protein plays a central role in the
       initiation of leukemogenesis. The two therapeutic agents,
       retinoic acid and arsenic, that induce clinical remissions in
       APL, both target the oncogenic fusion protein, representing the
       first example of oncogene-directed cancer therapy. This review
       focuses on the molecular mechanisms accounting for PML/
       RAR.alpha. degradation. Each drug targets a specific
       moiety of the fusion protein (RARα for  retinoic acid,
       PML for arsenic) to the proteasome. Moreover, both activate a common
       caspase-dependent cleavage in the PML part of the fusion protein.
       Specific molecular determinants (the AF2 transactivator domain of
       RARα for  retinoic acid and the K160 SUMO-binding site in
       PML for arsenic) are respectively implicated in RA- or arsenic-triggered
       catabolism. The respective roles of PML/RAR.alpha.
       activation versus its catabolism are discussed with respect to
       differentiation or apoptosis induction in the context of single or dual
       therapies.

L8     ANSWER 2 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on
```

STN
ACCESSION NUMBER: 2001269265 ESBIOBASE <<LOGINID::20100415>>
TITLE: Arsenic trioxide, a therapeutic agent for APL
AUTHOR(S): Zhang, Ting-Dong; Chen, Guo-Qiang; Wang, Zhu-Gang; Wang, Zhen-Yi; Chen, Sai-Juan; Chen, Zhu
CORPORATE SOURCE: Zhang, Ting-Dong (First Hospital, Harbin Medical University, 23 You Zheng Road, Nangang District, Harbin, 150001 (CN)); Chen, Guo-Qiang; Wang, Zhu-Gang; Wang, Zhen-Yi; Chen, Sai-Juan; Chen, Zhu (Shanghai Institute of Hematology, Rui Jin Hospital, Shanghai Second Medical University, 197, Rui Jin Road II, Shanghai 200025 (CN))
SOURCE: Oncogene (29 Oct 2001) Volume 20, Number 49 REV. IIS. 6, pp. 7146-7153, 73 refs.
CODEN: ONCNES ISSN: 0950-9232
DOI: 10.1038/sj.onc.1204762
COUNTRY OF PUBLICATION: United Kingdom
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2009
Last updated on STN: 1 Feb 2009

AN 2001269265 ESBIOBASE <<LOGINID::20100415>>
AB Acute promyelocytic leukemia (APL) is an interesting model in cancer research, because it can respond to the differentiation/apoptosis induction therapy using all-trans retinoic acid (ATRA) and arsenic trioxide (AS 2 O 3). Over the past 5 years, it has been well demonstrated that AS 2 O 3 induces a high complete remission (CR) rate in both primary and relapsed APL patients (around 85~90%). The side effects are mild to moderate in relapsed patients, while severe hepatic lesions have been found in some primary cases. After CR obtained in relapsed patients, chemotherapy in combination with AS 2 O 3 as post-remission therapy has given better survival than those treated with AS 2 O 3 alone. The effect of AS 2 O 3 has been shown to be related to the expression of APL-specific PML-RAR.alpha. oncoprotein, and there is a synergistic effect between AS 2 O 3 and ATRA in an APL mouse model. Cell biology studies have revealed that AS 2 O 3 exerts dose-dependent dual effects on APL cells. Apoptosis is evident when cells are treated with 0.5~2.0 μM of AS 2 O 3 while partial differentiation is observed using low concentrations (0.1~0.5 μM) of the drug. The apoptosis-inducing effect is associated with the collapse of mitochondrial transmembrane potentials in a thiol-dependent manner, whereas the mechanisms underlying APL cell differentiation induced by low dose arsenic remain to be explored. Interestingly, AS 2 O 3 over a wide range of concentration (0.1~2.0 μM) induces degradation of a key leukemogenic protein, PML-RAR.alpha., as well as the wild-type PML, thus setting up a good example of targeting therapy for human cancers .

L8 ANSWER 3 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2001191720 ESBIOBASE <<LOGINID::20100415>>
TITLE: A novel differentiation-inducing therapy for acute promyelocytic leukemia with a combination of arsenic trioxide and GM-CSF
AUTHOR(S): Muto, A.; Kizaki, M.; Kawamura, C.; Matsushita, H.; Fukuchi, Y.; Ikeda, Y.; Umezawa, A.; Yamada, T.; Hata, J.; Hozumi, N.; Yamato, K.; Ito, M.; Ueyama, Y.
CORPORATE SOURCE: Muto, A.; Kizaki, M.; Kawamura, C.; Matsushita, H.;

Fukuchi, Y.; Ikeda, Y. (Department of Internal Medicine, Division of Hematology, Keio University School of Medicine, Tokyo (JP)); Umezawa, A.; Yamada, T.; Hata, J. (Department of Pathology, Division of Hematology, Keio University School of Medicine, Tokyo (JP)); Hozumi, N. (Institute of Biological Science, Science University of Tokyo, Chiba (JP)); Yamato, K. (Department of Oral Function Restitution, Division of Oral Health Sciences, Tokyo Medical and Dental University, Tokyo (JP)); Ito, M. (Central Institute for Experimental Animals, Kanagawa (JP)); Ueyama, Y. (Department of Pathology, Tokai University, School of Medicine, Kanagawa (JP))

SOURCE: Leukemia (2001) Volume 15, Number 8, pp. 1176-1184, 44 refs.
CODEN: LEUKED ISSN: 0887-6924
DOI: 10.1038/sj.leu.2402162
COUNTRY OF PUBLICATION: United Kingdom
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2009
Last updated on STN: 1 Feb 2009

AN 2001191720 ESBIOBASE <<LOGINID::20100415>>

AB Arsenic trioxide (AS 2 O 3) effectively induces clinical remission via apoptosis in relapsed acute promyelocytic leukemia (APL). However, because this new anti-leukemic drug is also considered to be a poison, its possible adverse effects are a highly important issue related to its clinical use. We here investigated, both in vitro and in vivo, the effects of a combination of As 2 O 3 and GM-CSF as a novel therapeutic approach for the treatment of APL. Treatment of both retinoic acid (RA)-sensitive and -resistant APL cell lines (NB4 and UF-1 cells, respectively), as well as primary APL cells with a combination of As 2 O 3 and GM-CSF for 4 days resulted in inducing differentiation, but not apoptosis, to mature granulocytes. In addition, a combination of both agents induced degradation of the PML/RAR.alpha. protein. GM-CSF was found to be associated with increased tyrosine phosphorylation of Jak2 kinase in both NB4 and UF-1 cells, and a specific inhibitor of Jak2, AG490, completely blocked the ability of GM-CSF to prevent apoptosis and induce differentiation of As 2 O 3 -treated UF-1 cells. In in vivo analysis, As 2 O 3 induced differentiation of APL cells in a RA-resistant APL model of human GM-CSF-producing transgenic SCID mice that had a high level of human GM-CSF in their sera. In contrast, As 2 O 3 alone diminished tumors in UF-1 cells transplanted into NOD/SCID mice via induction of apoptosis. In conclusion, a combination of As 2 O 3 and GM-CSF appears to be a novel differentiation-inducing therapy in patients with APL, including relapsed or RA-resistant cases.

L8 ANSWER 4 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2001037372 ESBIOBASE <<LOGINID::20100415>>
TITLE: Granulocytic differentiation of human NB4 promyelocytic leukemia cells induced by all-trans retinoic acid metabolites
AUTHOR(S): Idres, N.; Benoit, G.; Flexor, M.A.; Lanotte, M.; Chabot, G.G.
CORPORATE SOURCE: Idres, N.; Benoit, G.; Flexor, M.A.; Lanotte, M.; Chabot, G.G. (Inst. Universitaire d'Hematologie, INSERM U496, Hopital Saint-Louis, 1 avenue Claude-Vellefaux,

75475 Paris (Cedex 10) (FR))
SOURCE: Cancer Research (15 Jan 2001) Volume 61, Number 2, pp. 700-705, 53 refs. CODEN: CNREA8 ISSN: 0008-5472
COUNTRY OF PUBLICATION: United States of America
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2009
Last updated on STN: 1 Feb 2009

AN 2001037372 ESBIOBASE <<LOGINID::20100415>>

AB The metabolism of all-trans retinoic acid (ATRA) has been reported to be partly responsible for the in vivo resistance to ATRA seen in the treatment of human acute promyelocytic leukemia (APL). However, ATRA metabolism appears to be involved in the growth inhibition of several cancer cell lines in vitro. The purpose of this study was to evaluate the in vitro activity of the principal metabolites of ATRA [4-hydroxyretinoic acid (4-OH-RA), 18-hydroxy-retinoic acid (18-OH-RA), 4-oxo-retinoic acid (4-oxo-RA), and 5,6-epoxy-retinoic acid (5,6-epoxy-RA)] in NB4, a human promyelocytic leukemia cell line that exhibits the APL diagnostic t(15;17) chromosomal translocation and expresses the PML-RAR.alpha. fusion protein. We established that the four ATRA metabolites were indeed formed by the NB4 cells in vitro. NB4 cell growth was inhibited (69-78% at 120 h) and cell cycle progression in the G 1 phase (82-85% at 120 h) was blocked by ATRA and all of the metabolites at 1 μM concentration. ATRA and its metabolites could induce NB4 cells differentiation with similar activity, as evaluated by cell morphology, by the nitroblue tetrazolium reduction test (82-88% at 120 h) or by the expression of the maturation specific cell surface marker CD11c. In addition, nuclear body reorganization to macropunctated structures, as well as the degradation of PML-RAR.mu., was found to be similar for ATRA and all of its metabolites. Comparison of the relative potency of the retinoids using the nitroblue tetrazolium reduction test showed effective concentrations required to differentiate 50% of cells in 72 h as follows: ATRA, 15.8 ± 1.7 nM; 4-oxo-RA, 38.3 ± 1.3 nM; 18-OH-RA, 55.5 ± 1.8 nM; 4-OH-RA, 79.8 ± 1.8 nM; and 5,6-epoxy-RA, 99.5 ± 1.5 nM. The ATRA metabolites were found to exert their differentiation effects via the RARα nuclear receptors, because the RARα-specific antagonist BMS614 blocked metabolite-induced CD11c expression in NB4 cells. These data demonstrate that the principal ATRA Phase 1 metabolites can elicit leukemia cell growth inhibition and differentiation in vitro through the RARα signaling pathway, and they suggest that these metabolites may play a role in ATRA antileukemic activity in vivo.

L8 ANSWER 5 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2000114309 ESBIOBASE <<LOGINID::20100415>>
TITLE: Arsenic trioxide therapy for relapsed acute promyelocytic leukemia: An useful salvage therapy
AUTHOR(S): Huang, Shang-Yi; Chen, Yao-Chang; Yang, Chih-Hsin
CORPORATE SOURCE: Huang, Shang-Yi; Chen, Yao-Chang (Department of Internal Medicine, National Taiwan University Hospital, Taipei (TW)); Chen, Yao-Chang (Department of Laboratory Medicine, National Taiwan University Hospital, Taipei (TW)); Chen, Yao-Chang (Departments of Internal Medicine, Laboratory Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei (TW)); Yang, Chih-Hsin (Department of Oncology,

National Taiwan University Hospital, Taipei (TW))
EMAIL: ycchen1@ha.mc.ntu.edu.tw
SOURCE: Leukemia and Lymphoma (2000) Volume 38,
Number 3-4, pp. 283-293, 72 refs.
CODEN: LELYEA ISSN: 1042-8194
COUNTRY OF PUBLICATION: United Kingdom
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2009
Last updated on STN: 31 Jan 2009

AN 2000114309 ESBIOBASE <<LOGINID::20100415>>

AB Arsenic trioxide (As2O3) was recently identified as a very potent agent against acute promyelocytic leukemia (APL). Intravenous infusion of 10 mg As2O3 daily for one to two months can induce significant complete remission (CR) of APL, and there is no cross drug-resistance between As2O3 and other antileukemic agents, including all-trans retinoic acid (ATRA). The CR rate of relapsed and/or refractory APL patients who received As2O3 treatment ranged from 52.3% to 93.3%. The median duration to CR ranged from 38 to 51 days, with accumulative As2O3 dosage of 340-430 mg. Although most adverse reactions of As2O3 treatment were tolerable, certain infrequent but severe toxicities related to As2O3 were observed, including renal failure, hepatic damage, cardiac arrhythmia and chronic neuromuscular degeneration, which should be monitored carefully. As2O3 can induce partial differentiation and subsequent apoptosis of APL cells through degradation of wild type PML and PML/RAR α chimeric proteins and possible anti-mitochondrial effects. Like the treatment of ATRA in APL, early relapses from As2O3 treatment within a few months were not infrequently seen, indicating that rapid emerging resistance to As2O3 can occur. Nevertheless, the PML/RAR α fusion protein was reported to disappear in some APL patients who received As2O3, and who might earn long-survival. However, the follow-up is still too short to draw the conclusion. Intriguingly, it has been shown that As2O3 can also induce apoptosis of other non-APL tumor cells with clinical achievable concentrations. However, the detailed molecular mechanisms are not yet fully understood. Further studies regarding to the pharmacological characters, clinical efficacies, toxicities, apoptogenic mechanisms, and spectrum of anti-tumor activity of As2O3 are warranted.

L8 ANSWER 6 OF 6 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1998037033 ESBIOBASE <<LOGINID::20100415>>
TITLE: Acute promyelocytic leukemia: Cellular and molecular basis of differentiation and apoptosis
AUTHOR(S): Chen, Zhu; Wang, Zhen-Yi; Chen, Sai-Juan
CORPORATE SOURCE: Chen, Zhu; Wang, Zhen-Yi; Chen, Sai-Juan (Shaghai Institute of Hematology, Ruljin Hospital, Shaghai Second Medical University, 197 Ruljin Road II, Shaghai, 200025 (CN)); Chen, Zhu (Shaghai Life Science Center, 320 Yue Yang Road, Shaghai, 200031 (CN))
SOURCE: Pharmacology and Therapeutics (Nov 1997)
Volume 76, Number 1-3, pp. 141-149, 56 refs.
CODEN: PHTHDT ISSN: 0163-7258
DOI: 10.1016/S0163-7258(97)00090-9
PUBL. ITEM IDENTIFIER: S0163725897000909
COUNTRY OF PUBLICATION: United States of America
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2009
Last updated on STN: 31 Jan 2009

AN 1998037033 ESBIOBASE <<LOGINID::20100415>>

AB Acute promyelocytic leukemia (APL) accounts for about 10% of all acute myeloid leukemias and is characterized by the chromosomal translocation t(15;17), which fuses the retinoic acid receptor (RAR) α gene to the promyelocytic leukemia (PML) gene. The PML-RAR α fusion gene plays an important role in leukemogenesis through antagonizing retinoic acid signalling and the regulatory pathways mediated by PML. APL is the first example of a human cancer that can be effectively treated with the differentiation inducer all-trans retinoic acid (ATRA). The therapeutic effect of ATRA in APL has been associated with the direct modulation of PML- RAR α, the restoration of the differentiation pathways regulated by wild- type RAR/ retinoid X receptor heterodimer and PML. More recently, a second drug, arsenic trioxide (As 2 O 3), has been discovered in China that also has a strong therapeutic effect against APL. A 2 O 3 can induce clinical remission in de novo or relapsed APL patients and has no cross-resistance with ATRA. It has dual effects on APL cells: preferential apoptosis at high concentration (0.5-2 μM) and partial differentiation at low concentration (0.1-0.5 μM). Modulation and degradation of PML-RAR α proteins can be induced by As 2 O 3 and probably contribute to these two effects. These studies lead to a model in which PMI-RAR α could be the target of both ATRA differentiation therapy and As 2 O 3 apoptosis therapy.

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	24.27	31.39

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 08:10:41 ON 15 APR 2010

63 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view search error messages that display as 0* with SET DETAIL OFF.

=> s lysosom? (s) destabiliz?

13	FILE AGRICOLA
29	FILE AQUALINE
48	FILE AQUASCI
28	FILE BIOENG
228	FILE BIOSIS
9	FILE BIOTECHABS
9	FILE BIOTECHDS
39	FILE BIOTECHNO
35	FILE CABA
273	FILE CAPLUS
2	FILE CONFSCI
2	FILE CROPU
1	FILE DDFB
19	FILE DDFU

```
         19   FILE DGENE
         22   FILE DISSABS
          1   FILE DRUGB
         31   FILE DRUGU
          2   FILE EMBAL
        203   FILE EMBASE
        175   FILE ESBIOBASE
          2   FILE FSTA
          3   FILE GENBANK
          1   FILE HEALSAFE
          2   FILE IFIPAT
          1   FILE KOSMET
        114   FILE LIFESCI
        186   FILE MEDLINE
         26   FILE OCEAN
         77   FILE PASCAL
          2   FILE PROUSDDR
        194   FILE SCISEARCH
        346   FILE TOXCENTER
        177   FILE USPATFULL
         29   FILE USPAT2
          1   FILE VETU
  59 FILES SEARCHED...
         29   FILE WATER
          7   FILE WPIDS
          7   FILE WPINDEX

  39 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L9   QUE LYSOSOM? (S) DESTABILIZ?

=> s L9 (s) retin###
          1   FILE AGRICOLA
          1   FILE BIOENG
          1   FILE BIOSIS
          2   FILE BIOTECHABS
          2   FILE BIOTECHDS
          2   FILE CABA
          3   FILE CAPLUS
          1   FILE DDFB
          2   FILE DDFU
          1   FILE DRUGB
          2   FILE DRUGU
          1   FILE EMBASE
          4   FILE ESBIOBASE
          5   FILE LIFESCI
          1   FILE MEDLINE
          6   FILE PASCAL
          1   FILE SCISEARCH
          2   FILE TOXCENTER
         17   FILE USPATFULL
          5   FILE USPAT2
          1   FILE WPIDS
  62 FILES SEARCHED...
          1   FILE WPINDEX

  22 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L10  QUE L9 (S) RETIN###

=> s L9 (s) (cancer or neoplas## or tumor?)
```

```
          3   FILE BIOENG
          7   FILE BIOSIS
          3   FILE BIOTECHABS
          3   FILE BIOTECHDS
          3   FILE BIOTECHNO
         15   FILE CAPLUS
          6   FILE DDFU
          8   FILE DGENE
  23 FILES SEARCHED...
          4   FILE DISSABS
          7   FILE DRUGU
          9   FILE EMBASE
         18   FILE ESBIOBASE
         11   FILE LIFESCI
          9   FILE MEDLINE
          9   FILE PASCAL
          2   FILE PROUSDDR
  49 FILES SEARCHED...
          9   FILE SCISEARCH
         10   FILE TOXCENTER
         43   FILE USPATFULL
         10   FILE USPAT2
          2   FILE WPIDS
          2   FILE WPINDEX

  22 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L11  QUE L9 (S) (CANCER OR NEOPLAS## OR TUMOR?)

=> s L11 and (stain### or mark### or releas###)
          1   FILE BIOENG
          3   FILE BIOSIS
          1   FILE BIOTECHABS
          1   FILE BIOTECHDS
          2   FILE BIOTECHNO
          5   FILE CAPLUS
  15 FILES SEARCHED...
          1   FILE DDFU
  23 FILES SEARCHED...
          2   FILE DISSABS
          5   FILE DRUGU
          4   FILE EMBASE
         11   FILE ESBIOBASE
  34 FILES SEARCHED...
          6   FILE LIFESCI
          4   FILE MEDLINE
          5   FILE PASCAL
          4   FILE SCISEARCH
          4   FILE TOXCENTER
  53 FILES SEARCHED...
         41   FILE USPATFULL
          9   FILE USPAT2
          1   FILE WPIDS
          1   FILE WPINDEX

  20 FILES HAVE ONE OR MORE ANSWERS,   63 FILES SEARCHED IN STNINDEX

L12  QUE L11 AND (STAIN### OR MARK### OR RELEAS###)

=> d rank
```

```
F1          41   USPATFULL
F2          11   ESBIOBASE
F3           9   USPAT2
F4           6   LIFESCI
F5           5   CAPLUS
F6           5   DRUGU
F7           5   PASCAL
F8           4   EMBASE
F9           4   MEDLINE
F10          4   SCISEARCH
F11          4   TOXCENTER
F12          3   BIOSIS
F13          2   BIOTECHNO
F14          2   DISSABS
F15          1   BIOENG
F16          1   BIOTECHABS
F17          1   BIOTECHDS
F18          1   DDFU
F19          1   WPIDS
F20          1   WPINDEX


=> fil f2, f4, f5, f8-f17
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 8.28      39.67

FILE 'ESBIOBASE' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'LIFESCI' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 Cambridge Scientific Abstracts (CSA)


FILE 'CAPLUS' ENTERED AT 08:17:38 ON 15 APR 2010
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2010 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'EMBASE' ENTERED AT 08:17:38 ON 15 APR 2010
Copyright (c) 2010 Elsevier B.V. All rights reserved.

FILE 'MEDLINE' ENTERED AT 08:17:38 ON 15 APR 2010

FILE 'SCISEARCH' ENTERED AT 08:17:38 ON 15 APR 2010
Copyright (c) 2010 The Thomson Corporation

FILE 'TOXCENTER' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'BIOSIS' ENTERED AT 08:17:38 ON 15 APR 2010
Copyright (c) 2010 The Thomson Corporation

FILE 'BIOTECHNO' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'DISSABS' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 ProQuest Information and Learning Company; All Rights Reserved.

FILE 'BIOENG' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 Cambridge Scientific Abstracts (CSA)
```

```
FILE 'BIOTECHABS' ACCESS NOT AUTHORIZED

FILE 'BIOTECHDS' ENTERED AT 08:17:38 ON 15 APR 2010
COPYRIGHT (C) 2010 THOMSON REUTERS

=> s L12
   9 FILES SEARCHED...
L13          47 L12

=> dup rem L13
PROCESSING COMPLETED FOR L13
L14          16 DUP REM L13 (31 DUPLICATES REMOVED)

=> s L14 and py<2004
   6 FILES SEARCHED...
L15           5 L14 AND PY<2004

=> d L15 ibib abs 1-5

L15    ANSWER 1 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on
       STN
ACCESSION NUMBER:       2003003379   ESBIOBASE <<LOGINID::20100415>>
TITLE:                  Pyridoxal isonicotinoyl hydrazone analogs induce
                        apoptosis in hematopoietic cells due to their
                        iron-chelating properties
AUTHOR(S):              Buss, Joan L.; Ponka, Prem; Neuzil, Jiri; Gellert,
                        Nina; Weber, Christian
CORPORATE SOURCE:       Buss, Joan L.; Ponka, Prem (Department of Physiology,
                        McGill University, Sir M. B. Davis Jewish Gen.
                        Hospital, 3755 chemin de la Cote-Ste-Catherine,
                        Montreal, Que. H3T 1E2 (CA)); Neuzil, Jiri (Division of
                        Pathology II, Faculty of Health Sciences, University
                        Hospital, Linkoping (SE)); Neuzil, Jiri; Gellert, Nina;
                        Weber, Christian (Inst. for Prev. of Cardiovasc. Dis.,
                        Ludwig Maximilians University, Munich (DE)); Neuzil,
                        Jiri (Heart Foundation Research Center, School of
                        Health Sciences, Griffith University, Southport, QLD
                        (AU)); Weber, Christian (Dept. of Cardiovasc. Molec.
                        Biology, University Hospital, Aachen (DE))
                        EMAIL: prem.ponka@mcgill.ca
SOURCE:                 Biochemical Pharmacology (15 Jan 2003) Volume
                        65, Number 2, pp. 161-172, 44 refs.
                        CODEN: BCPCA6  ISSN: 0006-2952
                        DOI: 10.1016/S0006-2952(02)01512-5
PUBL. ITEM IDENTIFIER:  S0006295202015125
COUNTRY OF PUBLICATION: United States of America
DOCUMENT TYPE:          Journal; Article
LANGUAGE:               English
SUMMARY LANGUAGE:       English
ENTRY DATE:             Entered STN: 2 Feb 2009
                        Last updated on STN: 2 Feb 2009
AN     2003003379   ESBIOBASE <<LOGINID::20100415>>
AB     Analogs of pyridoxal isonicotinoyl hydrazone (PIH) are of interest as
       iron chelators for the treatment of secondary iron overload and
       cancer. PIH, salicylaldehyde isonicotinoyl hydrazone (SIH), and
       2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone (NIH), the toxicity
       of which vary over two orders of magnitude, were selected for a study of
       their mechanisms of toxicity. PIH analogs and their iron complexes
       caused concentration- and time-dependent apoptosis in Jurkat T
       lymphocytes and K562 cells. Bcl-2 overexpression was partially
```

anti-apoptotic, suggesting mitochondrial mediation of apoptosis. Since the pan-caspase inhibitor zVAD-fmk did not reduce lysosomal and mitochondrial destabilization, these events occur upstream of caspase activation. In contrast, phosphatidylserine externalization and the development of apoptotic morphology were inhibited significantly, indicating the role of caspases in mediating these later events. Since overexpression of CrmA had no effect on apoptosis, caspase-8 is not likely involved. Fe 3+ complexes of SIH and NIH, which accumulated in 59 Fe-labeled mouse reticulocytes during incubation with the chelators, also caused apoptosis. BSA, which promotes release of the complexes from cells, reduced the toxicity of SIH and NIH, suggesting that the induction of apoptosis by PIH analogs involves toxic effects mediated by their Fe 3+ complexes. Moreover, analogs of these agents lacking the iron-chelating moiety were non-toxic. .COPYRGT. 2002 Published by Elsevier Science Inc.

L15 ANSWER 2 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2002214115 ESBIOBASE <<LOGINID::20100415>>
TITLE: Tumor necrosis factor-α-associated lysosomal permeabilization is cathepsin B dependent
AUTHOR(S): Werneburg, Nathan W.; Guicciardi, M. Eugenia; Bronk, Steven F.; Gores, Gregory J.
CORPORATE SOURCE: Werneburg, Nathan W.; Guicciardi, M. Eugenia; Bronk, Steven F.; Gores, Gregory J. (Mayo Med. School, Clinic/Foundation, 200 First St. SW, Rochester, MN 55905 (US))
SOURCE: American Journal of Physiology - Gastrointestinal and Liver Physiology (Oct 2002) Volume 283, Number 4 46-4, 44 refs.
CODEN: APGPDF ISSN: 0193-1857
COUNTRY OF PUBLICATION: United States of America
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2009
Last updated on STN: 1 Feb 2009

AN 2002214115 ESBIOBASE <<LOGINID::20100415>>

AB Cathepsin B (Cat B) is released from lysososomes during tumor necrosis factor-α (TNF-α) cytotoxic signaling in hepatocytes and contributes to cell death. Sphingosine has recently been implicated in lysosomal permeabilization and is increased in the liver by TNF-α. Thus the aims of this study were to examine the mechanisms involved in TNF-α-associated lysosomal permeabilization, especially the role of sphingosine. Confocal microscopy demonstrated Cat B-green fluorescent protein and LysoTracker Red were both released from lysosomes after treatment of McNtcp.24 cells with TNF-α/actinomycin D, a finding compatible with lysosomal destabilization. In contrast, endosomes labeled with Texas Red dextran remained intact, suggesting lysosomes were specifically targeted for permeabilization. LysoTracker Red was released from lysosomes in hepatocytes treated with TNF-α or sphingosine in Cat B(+/+) but not Cat B(-/-) hepatocytes, as assessed by a fluorescence-based assay. With the use of a calcein release assay in isolated lysosomes, sphingosine permeabilized liver lysosomes isolated from Cat B(+/+) but not Cat B(-/-) liver. C 6 ceramide did not permeabilize lysosomes. In conclusion, these data implicate a sphingosine-Cat B interaction inducing lysosomal destabilization during TNF-α cytotoxic signaling.

L15 ANSWER 3 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 2002107688 ESBIOBASE <<LOGINID::20100415>>
TITLE: Lysosomal destabilization in p53-induced apoptosis
AUTHOR(S): Yuan, Xi-Ming; Li, Wei; Brunk, Ulf T.; Dalen, Helge; Lotem, Joseph; Kama, Rachel; Sachs, Leo
CORPORATE SOURCE: Yuan, Xi-Ming; Li, Wei; Brunk, Ulf T. (Pathology II, Linkoping University, Linkoping 581 85 (SE)); Dalen, Helge (Department of Pathology, Gade Institute, University of Bergen, Bergen N-5021 (NO)); Lotem, Joseph; Kama, Rachel; Sachs, Leo (Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100 (IL))
EMAIL: yuan.ximing@inr.liu.se
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (30 Apr 2002) Volume 99, Number 9, pp. 6286-6291, 59 refs.
CODEN: PNASA6 ISSN: 0027-8424
DOI: 10.1073/pnas.092135599
COUNTRY OF PUBLICATION: United States of America
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 2009
Last updated on STN: 1 Feb 2009

AN 2002107688 ESBIOBASE <<LOGINID::20100415>>
AB The tumor suppressor wild-type p53 can induce apoptosis. M1-t-p53 myeloid leukemic cells have a temperature-sensitive p53 protein that changes its conformation to wild-type p53 after transfer from 37°C to 32°C. We have now found that these cells showed an early lysosomal rupture after transfer to 32°C. Mitochondrial damage, including decreased membrane potential and release of cytochrome c, and the appearance of apoptotic cells occurred later. Lysosomal rupture, mitochondrial damage, and apoptosis were all inhibited by the cytokine IL-6. Some other compounds can also inhibit apoptosis induced by p53. The protease inhibitor N-tosyl-L-phenylalanine chloromethyl ketone inhibited the decrease in mitochondrial membrane potential and cytochrome c release, the Ca 2+ -ATPase inhibitor thapsigargin inhibited only cytochrome c release, and the antioxidant butylated hydroxyanisole inhibited only the decrease in mitochondrial membrane potential. In contrast to IL-6, these other compounds that inhibited some of the later occurring mitochondrial damage did not inhibit the earlier p53-induced lysosomal damage. The results indicate that apoptosis is induced by p53 through a lysosomal-mitochondrial pathway that is initiated by lysosomal destabilization, and that this pathway can be dissected by using different apoptosis inhibitors. These findings on the induction of p53-induced lysosomal destabilization can also help to formulate new therapies for diseases with apoptotic disorders.

L15 ANSWER 4 OF 5 Elsevier Biobase COPYRIGHT 2010 Elsevier Science B.V. on STN

ACCESSION NUMBER: 1998098745 ESBIOBASE <<LOGINID::20100415>>
TITLE: Chromosomal instability is correlated with telomere erosion and inactivation of G2 checkpoint function in human fibroblasts expressing human papillomavirus type 16 E6 oncoprotein
AUTHOR(S): Filatov, Leonid; Golubovskaya, Vita; Hurt, John C.; Byrd, Laura L.; Phillips, Jonathan M.; Kaufmann,

William K.
CORPORATE SOURCE: Filatov, Leonid; Golubovskaya, Vita; Hurt, John C.; Byrd, Laura L.; Phillips, Jonathan M.; Kaufmann, William K. (Dept. of Pathol. and Lab. Medicine, Lineberger Compreh. Cancer Center, Univ. of N. Carolina at Chapel Hill, Chapel Hill, NC 27599-7295 (US))
SOURCE: Oncogene (9 Apr 1998) Volume 16, Number 14, pp. 1825-1838, 62 refs.
CODEN: ONCNES ISSN: 0950-9232
COUNTRY OF PUBLICATION: United Kingdom
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jan 2009
Last updated on STN: 31 Jan 2009
AN 1998098745 ESBIOBASE <<LOGINID::20100415>>
AB Cell cycle checkpoints and tumor suppressor gene functions appear to be required for the maintenance of a stable genome in proliferating cells. In this study chromosomal destabilization was monitored in relation to telomere structure, lifespan control and G2 checkpoint function. Replicative senescence was inactivated in secondary cultures of human skin fibroblasts by expressing the human papillomavirus type 16 (HPV-16) E6 oncoprotein to inactivate p53. Chromosome aberrations were enumerated during in vitro aging of isogenic control (F5neo) and HPV-16E6-expressing (F5E6) fibroblasts. We found that structural and numerical aberrations in chromosomes were significantly increased in F5E6 cells during aging in vitro and fluorescence in situ hybridization (FISH) analysis using chromosome-specific probes demonstrated the occurrence of rearrangements involving chromosome 4 and 6 in genetically unstable F5E6 cells. Flow and karyotypic analyses revealed increased and aneuploidy in F5E6 cells only at passages > 16, although these cells displayed defective mitotic spindle checkpoint function associated with inactivation of p53 at passages 5 and 16. G2 checkpoint function was confirmed to be gradually but progressively inactivated during in vitro aging of E6-expressing cells. Aging of F5neo fibroblasts was documented during in vitro passaging by induction of a senescence-associated marker, pH 6.0 lysosomal β-galactosidase. F5E6 cells displayed extension of in vitro lifespan and did not induce β-galactosidase at high passage. Erosion of telomeres during in vitro aging of telomerase-negative F5neo cells was demonstrated by Southern hybridization and by quantitative FISH analysis on an individual cell level. Telomeric signals diminished continuously as F5neo cells aged in vitro being reduced by 80% near the time of replicative senescence. Telomeric signals detected by FISH also decreased continuously during aging of telomerase-negative F5E6 cells, but telomeres appeared to be stabilized at passage 34 when telomerase was expressed. Chromosomal instability in E6-expressing cells was correlated ($P < 0.05$) with both loss of telomeric signals and inactivation of G2 checkpoint function. The results suggest that chromosomal stability depends upon a complex interaction among the systems of telomere length maintenance and cell cycle checkpoints.

L15 ANSWER 5 OF 5 DISSABS COPYRIGHT (C) 2010 ProQuest Information and Learning Company; All Rights Reserved on STN
ACCESSION NUMBER: 95:48382 DISSABS Order Number: AAI9527197
TITLE: DELIVERY OF MACROMOLECULES BY CATIONIC LIPOSOMES (DIOLEOYL PHOSPHATIDYLETHANOLAMINE)
AUTHOR: FARHOOD, HASSAN M. F. [PH.D.]; HUANG, LEAF [advisor]
CORPORATE SOURCE: THE UNIVERSITY OF TENNESSEE (0226)
SOURCE: Dissertation Abstracts International, (1994) Vol.

56, No. 4B, p. 1784. Order No.: AAI9527197. 169 pages.
DOCUMENT TYPE: Dissertation
FILE SEGMENT: DAI
LANGUAGE: English
ENTRY DATE: Entered STN: 19951031
Last Updated on STN: 19951031

AB Delivery of macromolecules to mammalian cells is a critical step for gene expression studies and for gene therapy. Cationic liposomes are simple vehicles for delivering macromolecules efficiently, reproducibly, and safely. To improve the efficiency and minimize the toxicity of cationic liposomes, liposomes containing cationic cholesterol derivatives and the phospholipid dioleoyl phosphatidyl-ethanolamine (DOPE) were designed and tested in transfection assays. Derivatives with a tertiary amine head group had efficient transfection activity, negligable cytotoxicity, and no protein kinase C-inhibition activity, while derivatives with a quaternary amine head group had no transfection activity, higher toxicity, and protein kinase C-inhibition activity. The membrane stabilizing phospholipid, dioleoyl phosphatidylcholine (DOPC), did not replace DOPE (a membrane destabilizer) in transfection. A new DNA delivery assay was developed that demonstrated the qualitative and quantitative requirement for DOPE in cationic liposome mediated transfection. The lysosomotropic agent chloroquine inhibition of transfection suggested that endocytosis is the major route of DNA delivery by cationic liposomes. Cationic liposomes were also used to deliver of the human immunodeficiency virus-1 trans-activator protein (tat), a model transcription factor that induces the expression of genes under the control of the virus promoter. Tat inefficient entry into the cytosolic compartment was improved with different cationic liposome formulations. Tat delivery was allowed by the inclusion of DOPE, but not DOPC, in the liposome formulations. Co-internalization of tat and cationic liposomes was required for maximal delivery activity implicating a common endocytic compartment from which tat was released into the cytosol, a conclusion based on the known membrane-disrupting function of DOPE and the natural endocytic fate of tat. To test the possibility of DNA and protein co-delivery, cells were transfected with tat protein complexed to a tat-responsive reporter DNA and cationic liposomes. The gene induction level was high and specific to tat-responsive promoter and the co-delivery system was applicable to different cell types using different cationic liposome formulations. This co-delivery strategy may be useful where transient and maximum gene expression may be necessary in certain applications such as cancer gene therapy.

=> logoff